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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,139	11/20/2001	Mark Thiede	640100-420	9767

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,139	THIEDE ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

This application is a 371 national stage filing of PCT/US99/26927, filed November 12, 1999, which claims benefit to provisional application 60/108,357, filed November 13, 1998.

Claims 1-27 are pending.

Examiner's Comments

In the appeals conference held September 13, 2005, it was decided that prosecution should be re-opened to supply new and relevant art not previously made of record.

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's appeal brief submission after final filed on July 22, 2005 has been entered.

Election/Restriction

Applicant's election of group II, claims 6-8, with traverse was acknowledged. It was noted that because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1-27 are pending. Claims 1-5, 9-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 6-8 are currently under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6-8 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a well asserted utility or a well established utility.

The specification teaches and provides evidence that mesenchymal stem cells can be transplanted *in utero* and that the implanted cells will distribute throughout the fetus, in some cases differentiating into cell types of organ in which they implanted. Based on the observed properties of the mesenchymal stem cells the specification proposes four potential clinical applications of: "1) large scale tissue engineering particularly for repair of musculoskeletal injury; 2) cellular therapy for diseases of mesenchymal origin such as muscular dystrophy, osteoporosis, osteogenesis imperfecta, and collagen disorders; 3) bone marrow conditioning to facilitate engraftment of autologous or allogeneic hematopoietic stem cells; and 4) gene therapy.

" (page 25). Further, the specification continues to speculate that "[P]renatal MSC transplantation may provide a "reservoir" of normal stem cells to replace defective cells as they become damaged in degenerative diseases with progressive cellular and organ damage." (page 25). The basis of the rejection focuses on the fact that while the specification reduces to practice the *in utero* transplantation of mesenchymal stem cells, and that the cells appear to distribute throughout the organs in the engrafted animal, the specification fails to provide a nexus wherein this phenomena will result in the proposed utilities.

With respect to tissue engineering the specification fails to provide any specific guidance on how a chimeric organ would or could be used in any context. Further, while it is acknowledged that mesenchymal cells implanted *in utero* will distribute into various tissues and organs in the fetus and be detectable in the resulting animal, the process by which this occurs is random and not subject any specific manipulation which would be consistent with generating a engineered tissue for further use. Moreover, with respect to using the engineered tissue for repair of musculoskeletal injury or in treating diseases of mesenchymal origin, there is no objective evidence that the implanted cells will obviate any specific damage that is present or will counter act any potential damage in diseases such as muscular dystrophy, osteoporosis, osteogenesis imperfecta or collagen disorders. For example, if an altered form of collagen is expressed by the cells of the host animal, it is unclear how providing a second source of collagen would alleviate any of the consequences of the altered collagen. The altered form of collagen would be present and the consequences of its presence would still be maintained resulting in the same condition associated with a given disorder. With respect to conditioning a tissue for engraftment, it may be that any resulting tissue from an animal implanted with

mesenchymal stem cells could possess antigens of the animal into which it would be transplanted, however this affect would not counter all the foreign antigens associated with the donor. Thus, while the tissue may contain cells that would not be recognized as foreign relative to the animal in which it is to be delivered, the potential for rejection is not counteracted relative to the foreign antigens that still exist within that tissue. Finally, with respect to the use of the method for gene therapy, it is unclear how the present method would be used to affect gene therapy. Currently, the art recognizes multiple limitations to affecting gene therapy including problems with gene delivery and gene expression, and it is unclear how the present method would be sued specifically to ameliorate any of the art recognized problems. Moreover, even in methods which appear to be affective in treating certain symptoms of a given disease, there is no guidance on how these gene therapy methods should be adapted with the methods as claimed.

It should be noted that the basis of the rejection does not focus on the clinical applicability of the claimed method, rather the fundamental applications as proposed. As reasoned above, each of the proposed utilities do not represent methodology common in the art and lack any specific real world context for use. It may be argued that the claimed method meets the utility requirement in that "an invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications" (*Carl Zeus Stiftung v. Renishaw PLC*, 945 F.2d 1173, 20 USPQ2d 1094 (Fed. Cir. 1991)). However, in the instant case, the claims lack utility not because they are incomplete, and not because they do not set forth the best or only way to accomplish a result, and not because they are not unique, but because they do not have either a well-established utility or a specific and substantial asserted utility.

Applicants have summarized the nature of the invention encompassed by the claims and each of the working examples provided in the instant specification noting that implanted mesenchymal stem cells were transplanted *in utero* and were able to implant and proliferate into several cell types in the resulting animal (pages 2-4). Applicants argue that "the results shown in the specification provide the basis for employing prenatal mesenchymal stem cell transplantation in order to provide a reservoir of normal stem cells to replace defective cells as they become damaged in degenerative diseases with progressive cellular and organ damage" (page 4 of Applicants' amendment and page 25 of the specification). Applicants argue that this is a specific and substantial utility, and that every utility need not be demonstrated nor operable citing *Ex parte Mark* (page 5). Applicants argue that in light of the working examples the office has failed to demonstrate that the claimed method has no utility. See Applicants' amendment and appeal brief. Applicants arguments have been fully considered, but not found persuasive.

Initially, it is noted that each of the proposed utilities taught in the specification were specifically discussed in the previous office action in the basis of the rejection. Applicants have focused on only one of the cited utilities that is MSC transplantation may provide a "reservoir" of normal stem cells to replace defective cells as they become damaged in degenerative diseases with progressive cellular and organ damage (page 25), and have not provided any discussion for the use in (1) large scale tissue engineering particularly for repair of musculoskeletal injury; 2) cellular therapy for diseases of mesenchymal origin such as muscular dystrophy, osteoporosis, osteogenesis imperfecta, and collagen disorders; 3) bone marrow conditioning to facilitate engraftment of autologous or allogeneic hematopoietic stem cells; and 4) gene therapy; each of which are in part representative of the ability of the implanted cells to act in a tissue or organ to

affect the desired treatment (previous office action page 3 and page 25 of the specification). Moreover, it is noted that the Examiner acknowledged the working examples in the specification but indicated that the basis of the rejection focuses on the fact that while the specification reduces to practice the *in utero* transplantation of mesenchymal stem cells, the specification fails to provide a nexus wherein the observed phenomena and the proposed utilities (bottom of page 3 of the previous office action). Further, it was noted that the basis of the rejection focuses on the fundamental applications as proposed by the specification, and not the potential clinical problems or applicability. Finally, it was acknowledged by the Examiner in part that a claimed invention need not teach the best method of accomplishing a particular task, and only need be useful to some extent or in accomplishing certain applications, citing *Carl Zeus Stiftung v. Renishaw.* However, contrary to Applicants' assertion the ability of a cell to implant and differentiate does not make it a reservoir of cells in cases of a degenerative disease. First, the specification does not teach what degenerative diseases can be affect by *in utero* implantation. Moreover, it does not provide a basis for why the implanted cell would be immune to the affects of any given degenerative disorder. For example, there are several degenerative disorders associated with the immune system wherein the immune system attacks antigens present on a cell such as in diabetes or MS, and it is unclear how an implanted cell will avoid the immune system in these diseases. In another example, the presence of an implanted cell does not make immune to external insults that result in a degenerative disorder such cirrhosis of the liver or affects of toxic or carcinogenic compounds. As noted in Applicants arguments the specification asserts a utility that has been thoroughly considered but demonstrated to neither substantial nor specific even in light of the working examples. Again, it is not contended that implantation of

cells will not occur, rather it is maintained that practicing this method has not specific nor substantial utility because these cells do not act as reservoirs in degenerative disease cases as asserted by the specification.

Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8 stand also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a well asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

As discussed above, the point of the rejection is not that mesenchymal cells will not implant themselves when administered *in utero*, rather that the specification fails to teach any specific or substantial circumstance to practice the method as claimed to provide a reservoir of stem cells or any of the other proposed utilities, in a fetus or resulting animal. The specification provides insufficient guidance and teaching on how to accomplish the proposed utilities specifically set forth. For example, the only substantive discussion of record has been drawn to the ability of the implanted cells to act as a reservoir of stem cells. Mackenzie *et al* (Cyrotherapy 2001 3(5):402-405) teach that implanted cells do undergo multilineage differentiation after in utero transplantaion, however summarize even in light of encouraging preliminary results further investigation is required for specfici applications (page 405, first column). Even today, while

the technical aspects of inserting cells *in utero* appear to be routine Santner-Nanan *et al.* (2005) teach that while research is ongoing, only a few avenuses of any therapy appear to provide potential benefit (see summary in abstract).

The high degree of unpredictability associated with the proposed utilities of the claimed method underscores the need to provide teachings in the specification that would provide the artisan with specific guidance or regimens for use of an engineered tissue that would result form the method or that achieve for example a therapeutic benefit in gene therapy methods. However, the specification does not provide such guidance. Without such guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Diukman *et al.* (J Reprod Med June 1992 37(6):515-520).

Claim 6 is broad encompassing methodology that simply requires the administration mesenchymal stem cells. It is known in the art and supported by the instant specification (page 2, lines 15-18), that mesenchymal stem cells reside in many sources including bone marrow and the blood. Claim 6 broadly reads on providing one of these sources wherein mesenchymal stem cells reside to a fetus *in utero*. Diukman *et al.* teach animal models where mouse, sheep and rhesus monkey receive *in utero* stem cell transplantation of bone marrow. Further, Diukman *et al.* teach that in light of animal studies, this methodology is being practiced in humans and that human trials are underway.

Claims 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Barnes *et al.* (J Med Genet Feb 1983 20(1) 41-45).

As discussed above, claim 6 broadly encompasses methodology that simply requires the administration mesenchymal stem cells, and the instant specification (page 2, lines 15-18) teaches that mesenchymal stem cells reside in many sources including bone marrow and the blood. Claim 6 broadly reads on providing one of these sources wherein mesenchymal stem cells reside to a fetus *in utero*. Barnes *et al.* teach animal models where human whole blood is injected intrauterine into rabbits and rhesus monkey. Each receive *in utero* stem cell transplantation present in the blood. Further, Barnes *et al.* teach that in light of animal studies, this methodology is under consideration for approaches to correct certain inherited diseasesi in humans.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

DRE Jones, Exper Opin Investig Drugs Nov 1998 7(11):1819-1824. Jones provides a review of the state of the art at the time of filing for the use of stem cell transplantation *in utero*.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

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